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MICE LACKING THE CIRCADIAN MODULATORS SHARP1 AND SHARP2 DISPLAY ALTERED SLEEP AND MIXED STATE ENDOPHENOTYPES OF PSYCHIATRIC DISORDERS

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INTRODUCTION: Increasing evidence suggests that clock genes may be implicated in a spectrum of psychiatric diseases, including sleep and mood related disorders as well as schizophrenia. The bHLH transcription factors SHARP1/DEC2/BHLHE41 and SHARP2/DEC1/BHLHE40 are modulators of the circadian system and SHARP1/DEC2/BHLHE40 has been shown to regulate homeostatic sleep drive in humans.

METHODS: In this study, we characterized *Sharp1* and *Sharp2* double mutant mice (S1/2$^{-/-}$) using online EEG recordings in living animals, behavioral assays, global gene expression profiling and bioinformatic modeling. Gene expression in human brains samples was performed with qRT-PCR.

RESULTS: EEG recordings revealed attenuated sleep/wake amplitudes and alterations of theta oscillations. Increased sleep in the dark phase is paralleled by reduced voluntary activity and cortical gene expression signatures reveal associations with psychiatric diseases. S1/2$^{-/-}$ mice display alterations in novelty induced activity, anxiety and curiosity. Moreover, mutant mice exhibit impaired working memory and deficits in prepulse inhibition resembling symptoms of psychiatric diseases. Network modeling indicates a connection between neural plasticity and clock genes, particularly for *SHARP1* and *PER1*, which are also significantly downregulated in the frontal cortex of schizophrenic patients.

CONCLUSIONS: Our findings support the hypothesis that abnormal sleep and certain (endo)phenotypes of psychiatric diseases may be caused by common mechanisms involving components of the molecular clock including SHARP1 and SHARP2

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